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PREDICTION

Better risk assessment with glycated hemoglobin instead of cholesterol in CVD risk prediction charts

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Abstract Traditional risk charts for the prediction of cardiovascular disease (CVD) include cholesterol parameters. We evaluated how models predict fatal CVD when cholesterol is replaced by glucose parameters. We used data from NHANES III, a US survey conducted 1988–1994 (follow-up until 2006); 15,454 participants (1,716 CVD deaths) were included. Based on the ESC SCORE method, we used age, sex, blood pressure, smoking and either of the following: (1) total cholesterol, (2) total-to-HDL-cholesterol, (3) glucose, (4) glycated hemoglobin (A1C). Scaled Brier score (BS), Nagelkerke's R^2 (NR) and integrated discrimination improvement (IDI) were used for model comparison. The ranking (best to worst) was: A1C (BS = 11.62 %; NR = 0.0865; IDI = 0.0091), glucose (11.16 %; 0.0734; 0.0067), total-to-HDL-cholesterol (9.97 %; 0.0547; 0.0010), cholesterol (9.75 %; 0.0484; 0, reference). Differences between models with cholesterol and glucose or A1C were statistically significant. This study suggests the use of A1C instead of cholesterol parameters in charts to assess CVD risk.

Keywords Glycated hemoglobin · Risk scores · Risk prediction · Mortality

Abbreviations

CVD	Cardiovascular disease
A1C	Glycated hemoglobin
NHANES	National Health and Nutrition Examination Survey

Introduction

Estimating the individual risk of cardiovascular disease (CVD) is traditionally based on age, sex, smoking status, blood pressure and total cholesterol or total-to-HDL-cholesterol. Derived risk prediction models and risk charts include the Framingham Risk Score or, from Europe, scores from Prospective Cardiovascular Münster Heart Study (PROCAM) or SCORE (Systematic COronary Risk Evaluation) [1–3]. Based on a large population sample from Switzerland with long mortality follow-up, cholesterol parameters contributed only little to prediction of mortality risk [4]. Traditional risk scores have been established decades ago. Meanwhile, new CVD risk factors have emerged. There is increasing evidence for glucose parameters being independent modifiable CVD risk factors [5]. Based on SCORE and adhering to a maximum of five variables displayed in the CVD risk chart, we used data from NHANES III to compare the traditional prediction model with models using glucose or glycated hemoglobin (A1C) instead of cholesterol.

Methods

We used data from the US-based NHANES III (Third National Health and Nutrition Examination Survey), conducted 1988–1994 and with mortality follow-up until December 31, 2006, originally including 20,050 individuals

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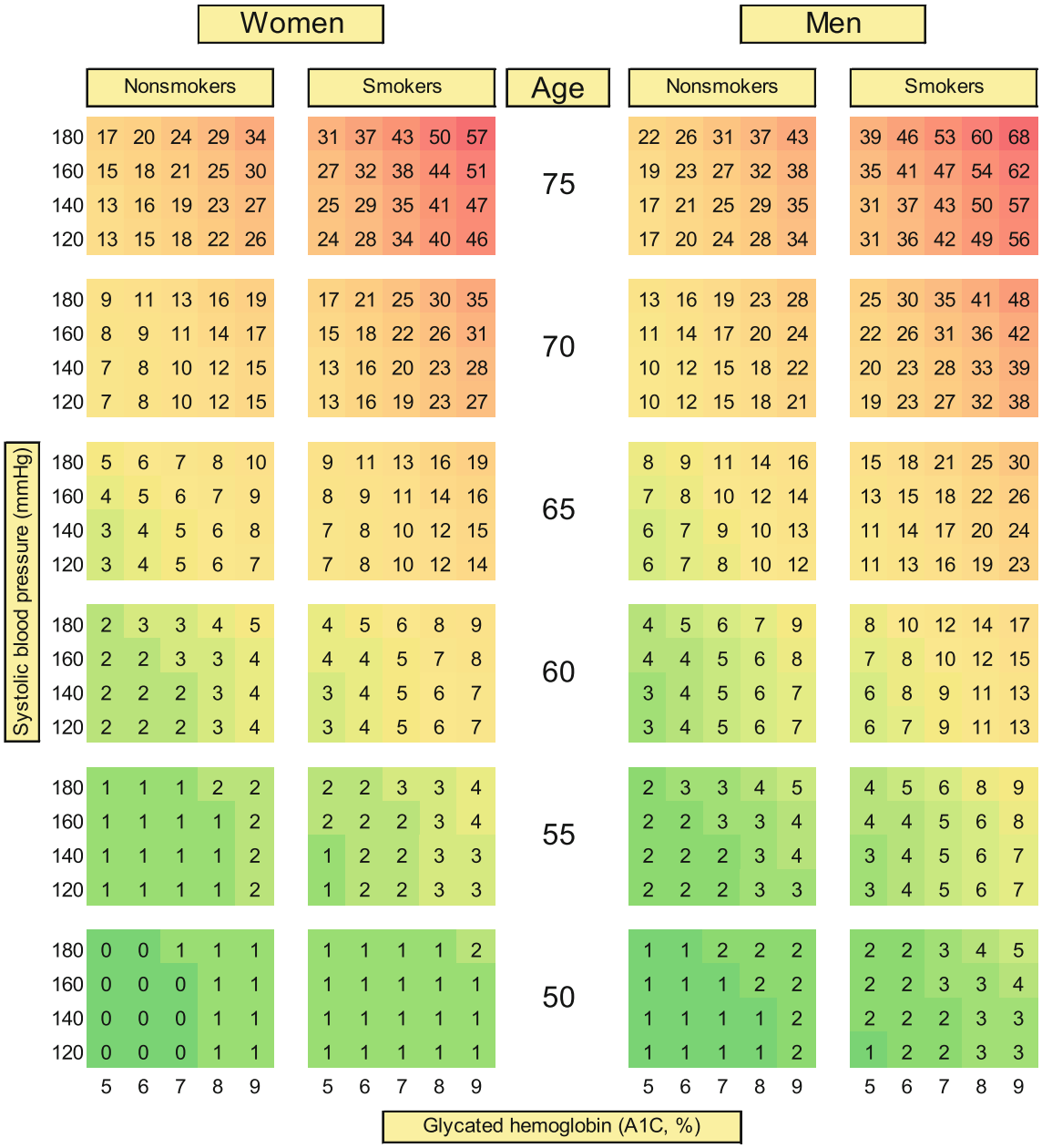

Fig. 1 Chart for absolute 10-year risk of fatal cardiovascular disease based on the model using A1C, 15,454participants of the NHANES III study, 1988–1994. NHANES III: Third National Health and Nutrition Examination Survey. Each risk percentage is calculated using a combination of given risk factor values. For example, a man aged 65, smoker, with a systolic blood pressure of 180 and a A1C of 9 % has an absolute risk (within the next 10 years) of fatal CVD of 30 %

[6] (see Web Annex, Table 1). Analysis was restricted to participants with all required variables (n = 15,454; 1,716 CVD deaths: ICD 9, 390–434; 436–459). We did not explicitly exclude participants with pre-existing diseases, but we performed sensitivity analyses without persons with known diabetes and/or CVD (see Web Annex, Fig. 1 and 2). Risk models were calculated with Weibull proportional hazards regression with age as time variable and two strata for sex [1]. Each of the four models included smoking status (binary) and systolic blood pressure. As preliminary analyses showed significant deviations from linearity, systolic blood pressure was modelled as restricted cubic spline with five knots (at 100, 113, 122, 135, 164 mmHg; see Web Annex, Fig. 3 and 4). For completion, one of the following variables was additionally included: total cholesterol, total-to-HDL-cholesterol, glucose, A1C. A final model included both A1C and cholesterol.

To compare the model fit, we used AIC, BIC and a version of Nagelkerke's R^2 by Royston [7]. In order to compare the predictive abilities of the models, we

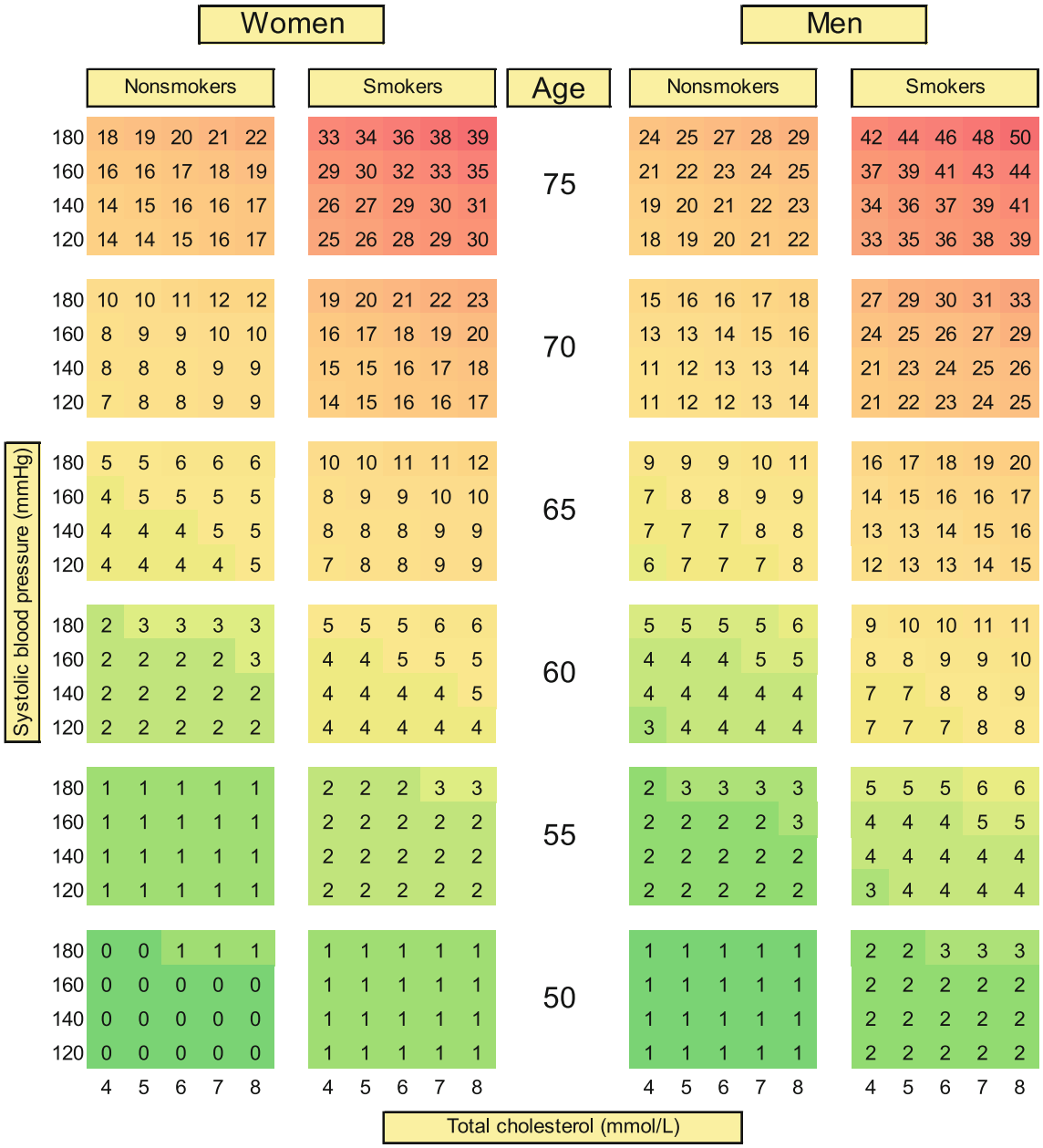

Fig. 2 Chart for absolute 10-year risk of fatal cardiovascular disease based on the model using total cholesterol, 15,454 participants of the NHANES III study, 1988–1994. NHANES III: Third National Health and Nutrition Examination Survey. Each risk percentage is calculated using a combination of given risk factor values. For example, a man aged 65, smoker, with a systolic blood pressure of 180 and a total cholesterol of 8 mmol/L has an absolute risk (within the next 10 years) of fatal CVD of 20 %

calculated the scaled mean cross-validated (leave-one-out) Brier score [8, 9] and the integrated discrimination improvement (IDI). A permutation test was used for the comparison of Brier scores from different models, and a Wald test was applied in the case of the IDI. The model with cholesterol was used as reference. The Brier score measures the mean squared difference between the risk score and the actual outcome. The lower this deviation, the better the respective risk prediction model. The Brier score covers both calibration, i.e. the agreement of the prediction with the true predictive distribution, and sharpness, i.e. the precision of the predictive distribution. The IDI is a measure of improvement in model performance and represents the difference in discrimination slopes of the competing models.

Analyses were performed with STATA 11 (Stata Corp, Texas, USA, 2009) and R (R Foundation for Statistical Computing, version 2.14.1).

Table 1 Estimated coefficients of modifiable risk factors of selected models with comparison measures

	Chart models (5 variables)				Separate model (6 variables)
	Total cholesterol	Total-to-HDL-cholesterol	Glucose	A1C	A1C + total cholesterol
Current smoking (yes/no)	1.994 (1.760; 2.260)	1.990 (1.756; 2.255)	2.046 (1.806; 2.318)	2.011 (1.775; 2.279)	2.010 (1.774; 2.278)
Total cholesterol (mmol/L)	1.058 (1.013; 1.104)				1.045 (1.001; 1.090)
Total-to-HDL-cholesterol (ratio)		1.073 (1.045; 1.102)			
Glucose (mmol/L)			1.087 (1.070; 1.105)		
Glycated hemoglobin (A1C, %)				1.226 (1.186; 1.267)	1.223 (1.184; 1.264)
Model comparison					
Scaled mean brier core	9.75 %	9.97 %	11.16 %	11.62 %	11.65 %
Nagelkerke's R^2	0.0484	0.0547	0.0734	0.0865	0.0879
AIC	2075	2057	2003	1965	1963
BIC	2152	2133	2079	2041	2047
Integrated discrimination improvement (IDI)	0 (reference)	0.0010 (0.16)	0.0067 (< 0.001)	0.0091 (< 0.001)	0.0089 (< 0.001)

Hazard ratios; figures in brackets are 95 % confidence intervals (coefficients) or *p* values (model comparison). Blood pressure was included as a restricted cubic spline with five knots (100, 113, 122, 135, 164 mmHg); see Fig. 3 and 4 in the Web Annex

Results

The predictive capacity of cholesterol and total-to-HDL-cholesterol was not significantly different (Table 1). Including cholesterol in addition to A1C did not improve the predictions. Risk charts derived from the analyses are shown in Figs. 1, 2. The A1C chart much better discriminated individuals with high and low CVD risk. Based on A1C and cholesterol, respectively, 11.8 and 11.2 % of the study population had a high CVD risk (≥20 %). Glucose and A1C predicted mortality significantly better than cholesterol even after exclusion of persons with known diabetes or CVD (Web Annex, Fig. 1 and 2).

Discussion

Our comparisons based on data from NHANES III suggest using A1C instead of cholesterol for CVD mortality risk charts. As shown by others, A1C not only serves as a predictor of diabetes, it has also the ability to predict death from CVD and from any cause and its predictiveness was better than that of glucose [5]. Traditional risk models do not consider glucose parameters as continuous variable. The PROCAM and the Framingham models include information about diabetes (yes/no) [2, 3] but this does not sufficiently map the potential impact of blood glucose on CVD. With dichotomization, mortality gradients below the threshold for diabetes are missed, which wastes prevention potential. In fact, excluding individuals with known diabetes only marginally attenuated absolute risks (see Web Annex, Fig. 1), suggesting that the A1C chart could also be used for primary prevention. Mortality risk increases at A1C concentrations ≥5.7 %. This threshold is lower when other CVD risk factors, e.g. high blood pressure or smoking, are present [5, 10]. This is also suggested by the risk chart derived from our analyses (Fig. 1).

One advantage of considering A1C in a continuous (instead of a dichotomized) form is that the CVD risk chart could be a tool for physicians helping to prevent or delay the onset of diabetes in persons with prediabetes (A1C 5.7–6.4 %) potentially reducing morbidity and premature death. The chart could be used to motivate individuals to follow lifestyle recommendations and to improve compliance. A1C can be lowered with physical activity, weight management and healthy diet and, thus, opens doors for lifestyle recommendations [11, 12]. Prediabetes can also be effectively treated with Metformin which decreases the rate of conversion from prediabetes to diabetes [11]. Caring for persons early in the pathway to diabetes may be much more effective than treating them once diabetes is established. This is not possible when the risk associated with increased A1C concentrations is only considered dichotomously. A1C can easily and inexpensively be measured and also be interpreted in the non-fasting state [5], thus facilitating screening procedures. Our analyses do not suggest that additional assessment of cholesterol parameters is necessary for risk assessment. In contrast, relying on cholesterol parameters only could mean to miss persons with increased CVD risk. In hypercholesterolemic patients, CVD mortality

could further be reduced with management of A1C [10]. This is also suggested when comparing the respective risk charts. However, whether reduction in A1C leads to a similar reduction in CVD as with improvement of cholesterol parameters (by lifestyle modification or medication) remains to be elucidated.

We conclude that CVD risk assessment including A1C may be superior to the traditional CVD risk chart with cholesterol. This needs to be confirmed with other populations.

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Conflict of interest The authors declare that they have no conflict of interest.

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